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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/505,228	08/20/2004	Kenichiro Kataoka	Q83093	2360

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EXAMINER	
COLEMAN, BRENDA LIBBY	
ART UNIT	**PAPER NUMBER**
1624	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/24/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/505,228	KATAOKA ET AL.	
	Examiner	Art Unit	
	Brenda L. Coleman	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-49* is/are pending in the application.

4a) Of the above claim(s) *9-12,34-43,48 and 49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,13-33 and 45-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/20/04 & 4/5/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-49 are pending in the application.

Election/Restrictions

1. Applicant's election with traverse of Group I in the reply filed on January 19, 2007 is acknowledged. The traversal is on the ground(s) that Group VI should be examined together with Group I. This is not found persuasive because the compounds of formula II are not a tautomer of formula I. A tautomer is where the double bond between the double O or double bond S becomes part of the ring and the hydrogen atom on the adjacent N binds to the O or S forming OH or SH. The compounds of Group VI are substituted by chlorine, bromine, iodine, or an alkyl or arylsulfonyl group which may be substituted, thus a search of the compounds of formula I would not include the compounds of formula II as urged by the applicants.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 9-12, 34-43, 48 and 49 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on January 19, 2007.

Information Disclosure Statement

3. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states,

"the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

4. The information disclosure statement filed on August 20, 2004 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 44-47 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In evaluating the enablement question, several factors are to be considered. *In re* Wands, 8 USPQ2d 1400 (Fed. Cir. 1988); *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5)

the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

HOW TO USE: The scope of "neurodegenerative diseases", "inflammatory diseases" or "cancer" cannot be deemed enabled. The notion that a compound could be effective against neurodegenerative diseases, inflammatory diseases or cancer in general is contrary to our current understanding of how pharmacologicals work. All attempts to find a pharmaceutical to treat neurodegenerative diseases, inflammatory diseases or cancer generally have thus failed. Additionally, instant claim language embraces disorders not only for treatment but for prevention which is not remotely enabled.

In view of the lack of direction provided in the specification regarding starting materials, the lack of working examples, and the general unpredictability of chemical reactions, it would take an undue amount of experimentation for one skilled in the art to make the claimed compounds and therefore practice the invention. To be enabling, the specification of a patent must teach those skilled in the art how to make and use the scope of the claimed invention without undue experimentation. The applicants' are not entitled to preempt the efforts of others. The test for determining compliance with 35 U.S.C. § 112, is whether the applicants have clearly defined their invention.

Additionally, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims where the compounds of formula I are used to inhibit glycogen-synthase-kinase (GSK-3), in addition to the treatment of a magnitude

of neurodegenerative diseases, autoimmune disease, etc., the claims also include the treatment of cancer. Evidence involving a single compound and two types of cancer was not found sufficient to establish the enablement of claims directed to a method of treating seven types of cancer with members of a class of several compounds In re Buting 163 USPQ 689. The remarkable advances in chemotherapy have seen the development of specific compounds to treat specific types of cancer. The great diversity of diseases falling within the "tumor" category means that it is contrary to medical understanding that any agent (let alone a genus of thousands of compounds) could be generally effective against such diseases. The intractability of these disorders is clear evidence that the skill level in this art is low relative to the difficulty of the task.

Where the utility is unusual or difficult to treat or speculative, the examiner has authority to require evidence that tests relied upon are reasonably predictive of in vivo efficacy by those skilled in the art. See In re Ruskin, 148 USPQ 221; Ex parte Jovanovics, 211 USPQ 907; MPEP 2164.05(a).

Patent Protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. Tossing out the mere germ of an idea does not constitute enabling disclosure. Genentech Inc. v. Novo Nordisk 42 USPQ2d 1001.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

6. Claims 1-8, 13-33 and 44-47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

a) Claims 1-8, 13-33 and 44-47 are vague and indefinite in that it is not known what is meant by "Derivative" which implies more then what is positively recited.

b) Claim 1 and claims dependent thereon are vague and indefinite in that it is not known what is meant by the brackets around the definitions of the substituents of formula I. Brackets are used to indicate that which the applicants would like to delete and are not recommend in claims other than those, which contain the nomenclature of species.

c) Claim 1 and claims dependent thereon are vague and indefinite in that it is not known what is meant by the periods used at the end of lines 8, 9 and 23 on page 192, lines 2 and 4 on page 193, lines 12 and 14 on page 196, and line 24 on page 198.

MPEP 608.01(m) Form of Claims [R - 3]

>The claim or claims must commence on a separate sheet and should appear after the detailed description of the invention.< While there is no set statutory form for claims, the present Office practice is to insist that each claim must be the object of a sentence starting with "I (or we) claim", "The invention claimed is" (or the equivalent). If, at the time of allowance, the quoted terminology is not present, it is inserted by the clerk. Each claim begins with a capital letter and ends with a period. **Periods may not be used elsewhere in the claims except for abbreviations**. See Fressola v. Manbeck, >36 USPQ2d 1211< (D.D.C. 1995). ** >Where a claim sets forth a plurality of elements or steps, each element or step of the claim should be separated by a line indentation, 37 CFR 1.75(i).<

d) Claim 1 and claims dependent thereon are vague and indefinite in that it is not known what is meant by the capital letter, which appears at the beginning of lines 6, 8, 9, 10 and 24 on page 192, line 3 on page 193, line 13 on page 196, and line 25 on page 198.

MPEP 608.01(m) Form of Claims [R - 3]

> >The claim or claims must commence on a separate sheet and should appear after the detailed description of the invention.< While there is no set statutory form for claims, the present Office practice is to insist that each claim must be the object of a sentence starting with "I (or we) claim", "The invention claimed is" (or the equivalent). If, at the time of allowance, the quoted terminology is not present, it is inserted by the clerk. Each claim begins with a capital letter and ends with a period. **Periods may not be used elsewhere in the claims except for abbreviations**. See Fressola v. Manbeck, >36 USPQ2d 1211< (D.D.C. 1995). ** >Where a claim sets forth a plurality of elements or steps, each element or step of the claim should be separated by a line indentation, 37 CFR 1.75(i).<

e) Claim 1 and claims dependent thereon are vague and indefinite in that it is not known what is meant by the definition of R^{30} to R^{32} which does not set forth those variables included within the definition.

f) Claim 3 and claims dependent thereon are vague and indefinite in that it is not known what is meant by the definition of R^1 and R^2 where R^1 and R^2 are as defined above. However, R^1 and R^2 are not defined within the claim.

g) Claim 28 recites the limitation "optionally substituted phenoxy group" in the definition of R^3. There is insufficient antecedent basis for this limitation in the claim.

h) Claim 30 and claims dependent thereon are vague and indefinite in that it is not known what is meant by the moiety -CH2- in the definition of G^1. It is believed that the applicants intended -CH_2-.

i) Claims 44, 46 and 47 are vague and indefinite in that the claim provides for the use of claimed compounds, but the claim does not set forth any steps involved in determining which are the diseases capable of being mediated by inhibiting the activity of GSK-3. It is unclear which diseases are mediated by inhibiting the activity of GSK-3. Determining whether a given disease responds or does not respond to such an inhibitor will involve undue experimentation. Suppose that a given drug, which has inhibitor properties in vitro, when administered to a patient with a certain disease, does not produce a favorable response. One cannot conclude that specific disease does not fall within this claim. Keep in mind that:

A. It may be that the next patient will respond. No pharmaceutical has 100% efficacy. What success rate is required to conclude our drug is a treatment? Thus, how many patients need to be treated? If "successful treatment" is what is intended, what criterion is to be used? If one person in 10 responds to a given drug, does that mean that the disease is treatable? One in 100? 1,000? 10,000? Will the standard vary depending on the current therapy for the disease?

B. It may be that the wrong dosage or dosage regimen was employed. Drugs with similar chemical structures can have markedly different

pharmacokinetics and metabolic fates. It is quite common for pharmaceuticals to work and or be safe at one dosage, but not at another that is significantly higher or lower. Furthermore, the dosage regimen may be vital --- should the drug be given e.g. once a day, or four times in divided dosages? The optimum route of administration cannot be predicted in advance. Should our drug be given as a bolus iv or in a time release po formulation. Thus, how many dosages and dosage regimens must be tried before one is certain that our drug is not a treatment for this specific disease?

C. It may be that our specific drug, while active in vitro, simply is not potent enough or produces such low concentrations in the blood that it is not an effective treatment of the specific disease. Perhaps a structurally related drug is potent enough or produces high enough blood concentrations to treat the disease in question, so that the first drug really does fall within the claim. Thus, how many different structurally related inhibitors must be tried before one concludes that a specific compound does not fall within the claim?

D. Conversely, if the disease responds to our second drug but not to the first, both of which are inhibitors in vitro, can one really conclude that the disease falls within the claim? It may be that the first compound result is giving the accurate answer, and that the success of second compound arises from some other unknown property, which the second drug is capable. It is common for a drug, particularly in the area of neurodegenerative, to work by many mechanisms. The history of psychopharmacology is filled with drugs, which were

claimed to be a pure receptor XYX agonist or antagonist, but upon further experimentation shown to affect a variety of biological targets. In fact, the development of a drug for a specific disease and the determination of its biological site of action usually precede linking that site of action with the disease. Thus, when mixed results are obtained, how many more drugs need be tested?

E. Suppose that our drug is an effective treatment of the disease of interest, but only when combined with some totally different drug. There are for example, agents in antiviral and anticancer chemotherapy, which are not themselves effective, but are effective treatments when the agents are combined with something else.

Consequently, determining the true scope of the claim will involve extensive and potentially inconclusive research. Without it, one skilled in the art cannot determine the actual scope of the claim. Hence, the claim is indefinite.

j) Claims 46 and 47 are vague and indefinite in that it is not known what is meant by "agent", which does not clarify whether the claim is limited to a compound, composition, or even complex composition.

k) Claims 46 and 47 are substantial duplicates of claim 1-46. A statement of intended use is not given material weight. Note In re Tuominen 213 USPQ 89.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-8, 13-33 and 44-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cao et al., U.S. Patent Application Publication No. 2003/0096813. The generic structure of Cao encompasses the instantly claimed compounds (see Formula I, page 2 and formula II-D page 11) as claimed herein. Examples II-D1, II-D2 and II-D3 differ only in the nature of the substituent on the N atom. Page 2, paragraph [0027] defines R^6 which is the substituent of the 7-membered ring is independently selected from R, oxo, halogen, CN, C(O)R, CO_2R, SO_2R, OR, SR, $N(R)_2$, NRC(O)R, $C(O)N(R)_2$, $NRCO_2R$, $OC(O)N(R)_2$, $NRSO_2R$ or SO_2NR. Thus, one of ordinary skill in the art at the time the invention was made would have been motivated to select for example CO_2H as well as other possibilities from the generically disclosed alternatives of the reference and in so doing obtain the instant compounds in view of the equivalency teachings outlined above.

Claim Objections

8. Claims 20-23, 31-33 and 44-47 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend on another multiple dependent claim. See MPEP § 608.01(n).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda L. Coleman whose telephone number is 571-272-0665. The examiner can normally be reached on 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brenda Coleman

Brenda L. Coleman
Primary Examiner Art Unit 1624
April 15, 2007